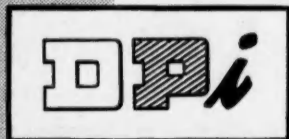


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POLYPHOSPHORIC ACID

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Polyphosphoric acid (PPA) is one of the most recent inorganic reagents to achieve prominence in synthetic organic chemistry. The name "Phospholeum" for PPA also appears, presumably because its preparation ($\text{H}_3\text{PO}_4 + \text{P}_2\text{O}_5$) resembles the preparation of fuming sulfuric acid ($\text{H}_2\text{SO}_4 + \text{SO}_3$), which is called "oleum." PPA is used extensively as a dehydrating cyclization agent; it has also shown amazing utility as a general acid catalyst (1). This versatility arises from its simultaneous strong dehydrating and otherwise mild properties. Although PPA does not exhibit the same strong affinity for water as sulfuric acid, neither does it cause extensive charring, nor does it react violently with hydroxylic compounds. Furthermore, under the conditions usually employed, there is no reaction analogous to sulfonation. For similar reasons, PPA is frequently preferred over phosphoric anhydride and the corrosive hydrogen fluoride. Because of its lower activity, PPA often causes fewer side reactions and thus produces fewer by-products than aluminum chloride. Happily, most PPA-catalyzed reactions show a definite increase in yield over the reactions employing the classical catalyst.

PPA can be prepared by stirring and heating *ortho*-phosphoric acid with sufficient phosphoric anhydride to give the resulting mixture an 82-85% P_2O_5 content (2). Commercial PPA is now available, however. It is known that PPA contains about 55% tripolyphosphoric acid, the remainder being *ortho*-phosphoric acid and other polyphosphoric acids (2). PPA is a glass when cold, a viscous liquid at room temperature, and is conveniently fluid at 60° C.

Although the procedures for its use vary widely, it is frequently taken in sufficient excess to serve as the solvent. Its solvent properties are good except in the case of hydrocarbons. Since higher yields of product are sometimes obtained upon increasing the amount of PPA used, the introduction of it as a catalyst should include trials in which it is used as the solvent also. Uhlig (3) describes a convenient preliminary test to determine the necessary reaction conditions. The compound (1 part) is added to PPA (10-30 parts) at room temperature. If the resulting solution darkens immediately, cooling is necessary; if it darkens slowly, room temperature may be used; otherwise, heating is necessary. The PPA can be readily disposed of, at least in the case of water-insoluble products, by pouring the reaction mixture into ice water.

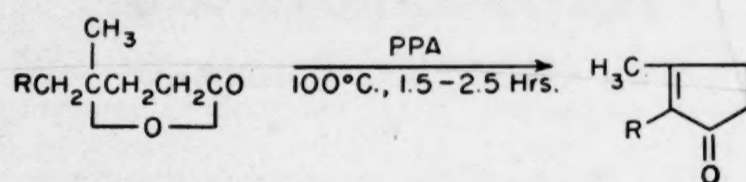
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Cyclizations

PPA was first used as a cyclization agent in 1938 (4), but an improved procedure, which appeared in 1945 (5), is now generally employed. Even so, PPA gained general attention only after its rediscovery by Snyder and co-workers in 1950 (6).

Examples of successful PPA-catalyzed ring closures appear in the literature in great number. Consequently, only representative examples will be presented in detail here, the others being included in the references, however. The ring closures are discussed in sequence from smallest to largest rings, first the carbocycles and second the heterocycles.

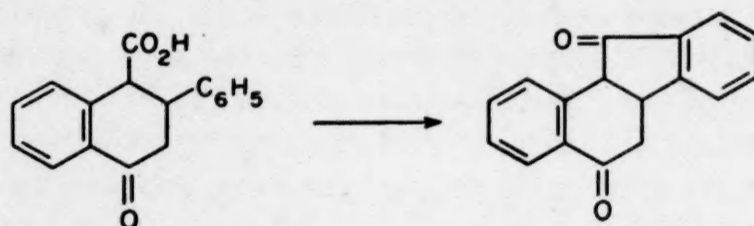
The procedure for the conversion of suitably constituted lactones to cyclopentenones using phosphoric anhydride has been known for many years; the yields were in the range of 20-50%. Rai and Dev (7) recently reported that, by replacing



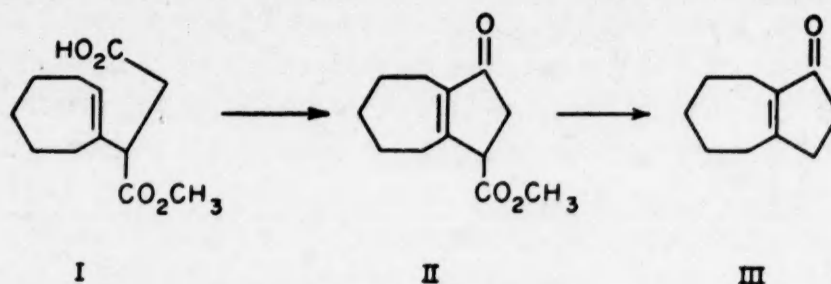
phosphoric anhydride with PPA, the cyclopentenones, where R is a straight alkyl chain containing from two to six carbon atoms, inclusive, are formed in the high yield of 90-97%.

Indanones have been obtained in some variety by the cyclization of β -arylpropionic acids and esters, with yields as high as 94% (6, 8, 9, 10, 11). Other highly substituted indanes, such as diethyl 4,5,6-trimethoxyindane-2,3-dicarboxylate, have also been synthesized by a PPA-catalyzed ring closure (11).

More complex ring systems have also been constructed by essentially the same reaction. Heating 1,2,3,4-tetrahydro-4-oxo-2-phenyl-1-naphthoic acid with PPA for 10 min. at 100° C. furnished 3,4,10,11-tetrahydro-3-oxo-1,2-benzofluorenone



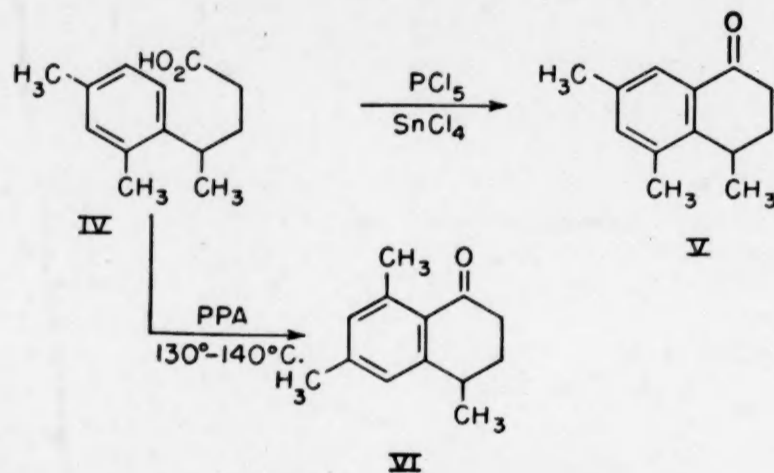
(12). The product (I) of the Stobbe condensation of suberone and dimethyl succinate cyclized in the presence of PPA to methyl 8-oxobicyclo[0,3,5]- $\Delta^{1,7}$ -decene-10-carboxylate (II), which, upon hydrolysis and decarboxylation, afforded cycloheptenocyclopentanone (III) in better yield than any other method (13).



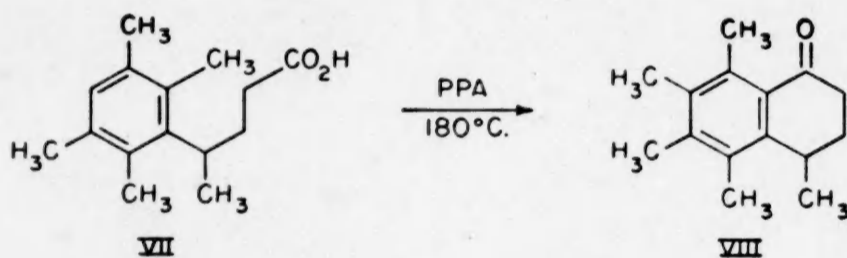
Tetralones have been prepared from aryl-alkyl acids in much the same manner as that for the 1-indanones and in similarly high yield. Heating γ -(2,4-dimethylphenyl)-butyric acid with PPA furnished 5,7-dimethyl-1-tetralone in yields to 93% (14).

Evans and Smith (14) determined the optimum conditions for this reaction to be roughly 150°-170° C. for 3 min. Prolonged or excessive heating produced various substituted, partially hydrogenated 10,11-benzofluoranthenes but with insufficient yields to be attractive synthetically (14). The PPA-catalyzed ring closure of arylbutyric acids has also been employed to synthesize methoxytetralones (15).

Trimethyltetralones have also been prepared (in about 70% yield) but their preparation involves an interesting rearrangement when PPA is used (16). It has been suggested that the valeric acid moiety of IV migrates, during heating, to a

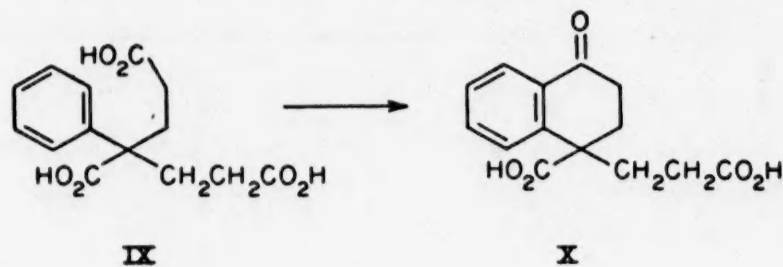


position in the xylene ring which is *meta* to the methyl groups, thus forming a more symmetrical molecule which subsequently ring-closes to VI. This contention was supported by the experimental fact that V, prepared by the phosphorus pentachloride-stannous chloride catalyzed cyclization of IV, was found unchanged after being heated with PPA. A disproportionation of the pentamethyl homolog, which is similar in effect but obviously different in origin, was also discovered (16). The



4,5,6,7,8-pentamethyl-1-tetralone (VIII) was isolated in 30% yield from among other products. In this instance, it appears that a methyl group actually migrated, since VIII may not be formed by the migration of the valeric acid moiety of VII alone, as in the case of VI. The possibility of methyl-group migration leads to the suggestion that PPA might be an excellent medium in which to conduct the Jacobson reaction of polymethylbenzenesulfonic acids.

In the cyclization of γ -carboxy (IX) or γ -cyano- γ -phenylpimelic acids to give the corresponding β -(1-substituted-1,2,3,4-tetrahydro-4-oxo-1-naphthyl)propionic acids (X), Hey and Nagdy (17) reported that PPA is not as efficacious a ring-closure



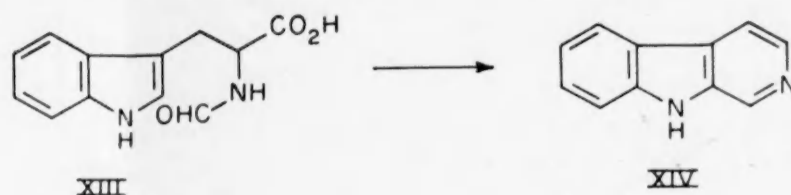
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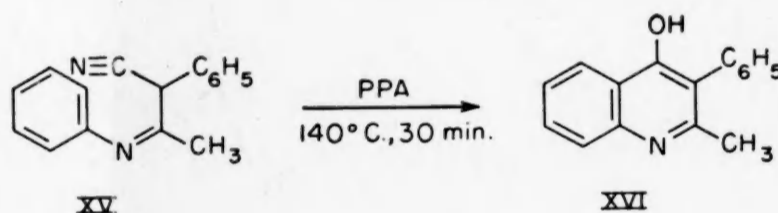
Snyder and co-workers found that a trace of POCl_3 was necessary in the PPA used in the Bishler-Napieralski synthesis of norharman (XIV) from N-formyl-dl-



tryptophane (XIII) (6). Norharman was produced in 36% yield when a trace of POCl_3 was present and was not formed at all in its absence.

The Pechmann synthesis of coumarins from resorcinol and substituted acetoacetic esters has been reported to take place in 80-95% yields (11). PPA at 75°-80° C. for 20 min. was employed, using several different esters containing a combination of methyl and phenyl groups.

The synthesis of 2-methyl-3-phenyl-4-quinolinol (XVI) by the cyclization of the anil (XV) formed by the condensation of aniline with α -acetyl- α -tolunitrile has recently appeared (27). The anil formation, catalyzed by acetic acid, occurred in 71% yield, and the PPA-catalyzed second step occurred in 79% yield. When the



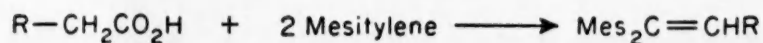
two-step process was carried out in one step using PPA alone, the yield of XVI was 39%.

The failure of PPA to replace sulfuric acid in the Skraup reaction (16) and its moderately successful use in a modified Pomeranz-Fritsch reaction have both been reported (28).

Acylations

Acylations of aromatic compounds also occur readily in the presence of PPA. This, of course, is the intermolecular counterpart of many of the intramolecular reactions which were discussed earlier. PPA is especially useful in the acylation of aryl-alkyl ethers because of the absence of ether cleavage. Thus, acetic anhydride or acetic acid at 45° C. for 3 hr. acylates the trimethyl ether of pyrogallol, giving 2,3,4-trimethoxyacetophenone in 93% yield (20). Similarly, benzoic acid gives 2,3,4-trimethoxybenzophenone in 92% yield (20). Japanese workers, headed by Nakazawa (29), are studying PPA-catalyzed acylations of phenols and related compounds. According to these workers, acetic acid triacetylates phloroglucinol, giving 1,3,5-triacetylphloroglucinol, while, under similar conditions, benzoic acid gives only phloroglucinol tribenzoate.

It has been reported (6) that mesitylene was acylated and the product then reacted with another mole of mesitylene in the presence of PPA to provide an ethylenic hydrocarbon. Acetic acid, propionic acid, and butyric acid furnished 9% of



1,1-dimesitylethylene, 39% of 1,1-dimesitylpropene, and 48% of 1,1-dimesityl-

butene, respectively. On the other hand, chloroacetic acid gave only mono- and bischloroacetylmesitylene.

The PPA-catalyzed Fries rearrangement seemed to have nothing to recommend it over the aluminum chloride-catalyzed rearrangement (20). For example, phenyl acetate, heated 1.5 hr. with PPA, furnished 4-hydroxyacetophenone in 35-50% yield. The use of higher temperatures resulted in lower yields.

(To be continued)

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